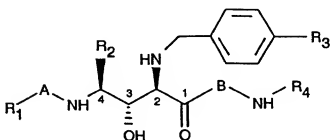


Claims:

1. Use of a 2,4-diamino-3-hydroxycarboxylic acid of formula I



wherein

A and B independently represent a bond or an unsubstituted or substituted amino acyl moiety;

R₁ represents hydrogen; an amino protecting group; or a group of formula R₅Y- wherein R₅ represents hydrogen or an unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl group; and Y represents -CO-; -NH-CO-; -NH-CS-; -SO₂-; -O-CO-; or -O-CS-;

R₂ represents the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl;

R₃ represents halogen, alkyl, alkoxy or hydroxyalkoxy; and

R₄ represents 2(R)-hydroxyindan-1(S)-yl; (S)-2-hydroxy-1-phenylethyl; or 2-hydroxy-benzyl unsubstituted or substituted in 4-position by methoxy;

in free form or in pharmaceutically acceptable salt or complex form in the manufacture of a pharmaceutical composition for the treatment of a proliferative disease responsive to an inhibition of the multicatalytic proteasome complex.

2. Use of a 2,4-diamino-3-hydroxycarboxylic acid of formula I according to claim 1, wherein

A and B independently represent a bond or an amino acyl moiety, which is unsubstituted or substituted by alkyl or alkoxy-carbonylalkyl;

R₁ represents hydrogen; an amino protecting group; or a group of formula R₅Y- wherein R₅ represents hydrogen or an unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl group; and Y represents -CO-; -NH-CO-; -NH-CS-; -SO₂-; -O-CO-; or -O-CS-;

R₂ represents the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl;

R₃ represents halogen, alkyl, alkoxy or hydroxyalkoxy; and

R₄ represents 2(R)-hydroxyindan-1(S)-yl; (S)-2-hydroxy-1-phenylethyl; or 2-hydroxybenzyl unsubstituted or substituted in 4 position by methoxy.

3. Use of a 2,4-diamino-3-hydroxycarboxylic acid of formula I according to claim 1, wherein A and B independently represent a bond or an amino acyl moiety, which is unsubstituted or substituted by alkyl or alkoxy carbonylalkyl;

R₁ represents hydrogen; an amino protecting group; or a group of formula R₅Y- wherein R₅ represents hydrogen or an unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl group; and Y represents -CO-; -NH-CO-; -NH-CS-; -SO₂-; -O-CO-; or -O-CS-;

R₂ represents arylalkyl;

R₃ represents halogen, alkyl, alkoxy or hydroxyalkoxy; and

R₄ represents 2-hydroxybenzyl which is unsubstituted or substituted in 4 position by methoxy.

4. Use of a 2,4-diamino-3-hydroxycarboxylic acid of formula I according to claim 1, wherein A and B independently represent an amino acyl moiety, which is unsubstituted or substituted by C₁-C₄alkyl or C₁-C₄alkoxy carbonyl C₁-C₄alkyl;

R₁ represents hydrogen or a group of formula R₅Y- wherein

R₅ represents hydrogen; C₁-C₄alkyl which is unsubstituted or substituted by phenoxy, hydroxy or amino; C₂-C₄alkenyl; C₂-C₄alkynyl; C₆-C₁₀aryl; C₇-C₁₂arylalkyl which is unsubstituted or substituted by hydroxy, C₁-C₄alkyl, amino or C₁-C₄alkyl amino; pyridyl C₁-C₄alkyl; and

Y represents -O-CO- or -CO-;

R₂ represents C₇-C₁₂arylalkyl;

R₃ represents halogen, C₁-C₄alkyl, C₁-C₄alkoxy or hydroxy C₁-C₄alkoxy; and

R₄ represents 2-hydroxybenzyl which is unsubstituted or substituted in 4 position by methoxy.

5. Use of a 2,4-diamino-3-hydroxycarboxylic acid of formula I according to claim 1, wherein

A and B independently represent an amino acyl moiety, which is unsubstituted or substituted by C₁-C₄alkyl or C₁-C₄alkoxycarbonyl C₁-C₄alkyl

R₁ represents hydrogen or a group of formula R₅Y- wherein

R₅ represents hydrogen; C₁-C₄alkyl which is unsubstituted or substituted by phenoxy, hydroxy or amino; C₂-C₄alkenyl; C₂-C₄alkinyl; C₆-C₁₀aryl; C₇-C₁₂arylalkyl which is unsubstituted or substituted by hydroxy, C₁-C₄alkyl, amino or C₁-C₄alkyl amino; pyridyl C₁-C₄alkyl; and

Y represents -O-CO- or -CO-;

R₂ represents C₇-C₁₂arylalkyl;

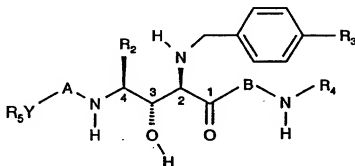
R₃ represents C₁-C₄alkoxy; and

R₄ represents 2-hydroxybenzyl substituted in 4 position by methoxy.

6. A method of treatment of warm-blooded animals, including humans, in which a therapeutically effective dose of a 2,4-diamino-3-hydroxycarboxylic acid of the formula I, in which the symbols and substituents have the meaning as given in claim 1, in free form or in pharmaceutically acceptable salt or complex form is administered to such a warm-blooded animal suffering from a proliferative disease responsive to an inhibition of the multicatalytic proteasome complex.

7. The method of claim 6 wherein the therapeutically effective dose inhibits cell proliferation in a tumor.

8. A compound of the formula I*,



I*

wherein

A and B independently represent an unsubstituted or substituted amino acyl moiety;

R₂ represents arylalkyl;

R₃ represents halogen, alkyl, alkoxy or hydroxyalkoxy;

R₄ represents 2-hydroxy-benzyl unsubstituted or substituted in 4 position by methoxy; and

R₅ represents arylalkyl and

Y represents -CO-; or

R₅ represents alkyl substituted by cycloalkyl, naphthyl, pyridyl or phenyl in which phenyl is substituted by alkyl or amino; and

Y represents -O-CO-;

or a pharmaceutically acceptable salt thereof.

9. A compound of the formula I* according to claim 8, wherein

A and B independently represent L-tert.-leucine, L-valine, L-glutaminic acid methyl ester or glycine;

R₂ represents arylalkyl;

R₃ represents alkoxy;

R₄ represents 2-hydroxy-4-methoxybenzyl; and

R₅ represents arylalkyl and

Y represents -CO-; or

R₅ represents alkyl substituted by cycloalkyl, naphthyl, pyridyl or phenyl in which phenyl is substituted by alkyl or amino; and

Y represents -O-CO-;

or a pharmaceutically acceptable salt thereof.

10. A compound of the formula I* according to claim 8, wherein

A and B independently represent L-tert.-leucine, L-valine, L-glutaminic acid methyl ester or glycine;

R₂ represents C₇-C₁₂arylalkyl;

R₃ represents C₁-C₄alkoxy;

R₄ represents 2-hydroxy-4-methoxybenzyl; and

R₅ represents C₇-C₁₂arylalkyl and

Y represents -CO-; or

R₅ represents C₁-C₄alkyl substituted by C₅-C₇cycloalkyl, naphthyl, pyridyl or phenyl in which phenyl is substituted by C₁-C₄alkyl or amino; and

Y represents -O-CO-;

or a pharmaceutically acceptable salt thereof.

11. A compound of formula I* according to claim 8 selected from the group of compounds consisting of

- 4-[4-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-3-hydroxy-2-(4-methoxy-benzyl-amino)-5-phenyl-pentanoylamino]-4-(2-hydroxy-4-methoxy-benzylcarbamoyl)-butyric acid methyl ester;
- {1-[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzyl-carbamoyl)-2-methyl-propyl-carbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl}-carbamic acid naphthalen-1-ylmethyl ester;
- {1-[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2-methyl-propyl-carbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl}-carbamic acid naphthalen-2-ylmethyl ester;
- {1-[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2-methyl-propyl-carbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl}-carbamic acid pyridin-4-ylmethyl ester;
- {[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2-methyl-propyl-carbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-methyl}-carbamic acid benzyl ester;
- {1-[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2,2-dimethyl-propyl-carbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester;

and the pharmaceutically acceptable salts of these compounds.

12. A compound of formula I* according to claim 8, which is

- 4-[4-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-3-hydroxy-2-(4-methoxy-benzyl-amino)-5-phenyl-pentanoylamino]-4-(2-hydroxy-4-methoxy-benzylcarbamoyl)-butyric acid methyl ester

or a pharmaceutically acceptable salt of this compound.

13. A compound of formula I* according to claim 8 selected from the group of compounds consisting of

- 4-[3,3-Dimethyl-2-(2-naphthalen-1-yl-acetylamino)-butyrylamino]-3-hydroxy-2-(4-methoxy-benzylamino)-5-phenyl-pentanoic acid [1-(2-hydroxy-4-methoxy-benzyl-

carbamoyl)-2-methyl-propyl]-amide;

{1-[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2-methyl-propylcarbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl]-carbamic acid 3-methylbenzyl ester;

4-{2-[3-(3-Amino-phenyl)-propionylamino]-3,3-dimethyl-butyrylamino]-3-hydroxy-2-(4-methoxy-benzylamino)-5-phenyl-pentanoic acid [1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2-methyl-propyl]-amide;

{1-[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2-methyl-propylcarbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl]-carbamic acid 3-amino-benzyl ester;

{1-[1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzyl-carbamoyl)-2-methyl-propylcarbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl]-carbamic acid 3,5-dimethyl-benzyl ester;

{1-[(1-Benzyl-2-hydroxy-3-[1-(2-hydroxy-4-methoxy-benzylcarbamoyl)-2-methyl-propylcarbamoyl]-3-(4-methoxy-benzylamino)-propylcarbamoyl]-2,2-dimethyl-propyl]-carbamic acid cyclohexylmethyl ester;

and the pharmaceutically acceptable salts of these compounds.

14. A compound of formula I* according to claim 8 or a pharmaceutically acceptable salt of such a compound for use in the therapeutic treatment of the human or animal body.

15. A pharmaceutical composition comprising a compound of formula I* according to claim 8 or a pharmaceutically acceptable salt of such a compound together with a pharmaceutical carrier.